Effects of reserpine on amino-acid excretion in patients with migraine¹

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Typical migraine headaches have been consistently induced by the administration of reserpine to migraineous patients. In such patients an increase in urinary excretion of histidine and lysine has been reported to accompany attacks of migraine (Kimball and Friedman, 1961; Menkes, 1964). These amino-acids have also been found in the oedema fluid which accumulates near the temporal arteries of patients during attacks of migraine headaches (Wolff, 1963). These observations suggest that reserpine-induced headaches may be a means of studying migraine. The present study, therefore, was undertaken to test whether the aminoaciduria of spontaneous migraine could be reproduced with reserpine; and to study what relation, if any, exists between the aminoaciduria and the clinical symptoms of migraine headaches.

SUBJECTS AND METHODS

Twenty subjects were studied: seven normal patients; five migraineous patients with spontaneous headaches; and eight migraineous patients with reserpine-induced headaches. The criteria for the diagnosis of migraine were paroxysmal unilateral headaches with or without prodromata, associated nausea, family history, and the absence of other neurological disease. The patients with migraine receiving reserpine were hospitalized in the Metabolic Research Unit of New York University School of Medicine. During the period of study, these hospitalized patients received a standard hospital diet from which were eliminated coffee, tea, and fruits, for purposes of other simultaneously conducted studies (Kimball and Bauer, 1966). Urine was collected in eight-hour fractions daily, and a few granules of thymol and 6 ml. of concentrated HCl were added to each specimen. Aliquots were stored at -10 to -20° Centigrade.

Each patient served as his own control. Paired urine samples obtained from the same patient during corresponding times of collection were analyzed for histidine concentration. One sample represents the histidine excretion during a headache period following the administration of 2.5 mg. of reserpine (i.m.), the other a control period during which there was no headache or reserpine administration. Histidine is reported as $\mu\text{g./mg. creatin-}$

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ine. Samples of urine, each of 10 lambda, and histidine standard (1.25 mg./ml.) were applied in a thin half-inch long horizontal line on Reeve Angel SA-2 ion exchange resin-impregnated paper. The paper was subjected to descending chromatography in a 0.4N acetate buffer (pH 5.1) for four hours. The developed chromatograms were dried in an oven at 60°C. and passed through a solution composed of 0.8 g. ninhydrin and 0.12 g. hydrindantin dissolved in 30 ml. methyl cellulose and 10 ml. in sodium acetate buffer (pH 5.5) (Moore and Stein, 1954). The chromatograms were again dried at 60°C. for one hour and left overnight at room temperature for maximal colour development. The paper was cut into strips parallel to the developing chromatogram and mounted in a Photovolt Densicord with a green filter. The concentration of histidine was calculated by integration with a Photovolt Integrator model 49 of the graphically recorded optical densities. With care taken to reduce background density to a minimum, and to preserve a uniform horizontal spot length of $\frac{1}{8}$ inch, the concentration of histidine expressed as a fraction of the standard was determined with a precision of 5 to 10%.

RESULTS

Increase in urinary histidine was observed following headaches in migraineous patients (Table I). P values determined by the Student test showed the increase in histidine to be significant (Snedecor, 1956). Comparable values for patients with spontaneous headaches are shown in Table II. The chromatographic definition of lysine was not adequate for quantitation, though there appeared in each case to be a qualitative increase. The effects of intra-

TABLE I
EFFECTS OF RESERPINE ON URINARY HISTIDINE IN MIGRAINOUS SUBJECTS¹

Patient	No Headache	Headache	Difference
SU	197	413	216
KF	158	320	162
CM	163	308	145
AS	146	274	128
PP	133	292	159
CB	119	316	197
DF	370	585	215
DE	132	421	289
Mean	177	366	189

¹Values expressed as $\mu\text{g./mg. creatinine}$

muscular reserpine on histidine excretion in normal controls is summarized in Table III. In addition to these control patients, in three patients, prolonged fast, hypoglycaemia, and digitalis intoxication were without demonstrable effect on histidine excretion.

TABLE II

URINARY HISTIDINE EXCRETION IN MIGRAINOUS SUBJECTS DURING SPONTANEOUS HEADACHE AND NON-HEADACHE PERIODS¹

Patient	No Headache	Headache	Difference
PL	178	352	174
SW	294	400	106
MI	391	840	449
AP	108	353	245
HO	132	230	98
Mean	221	435	214

¹Values expressed as $\mu\text{g./mg. creatinine}$

TABLE III

URINARY HISTIDINE EXCRETION IN NON-MIGRAINOUS SUBJECTS BEFORE AND AFTER RESERPINE ADMINISTRATION¹

Patient	Reserpine		Difference
	Free Period	Administration Period	
MG	510	186	-324
KH	337	235	-102
JC	369	420	+41
MM	332	264	-68
PL	175	172	-3
FS	98	153	+55
Mean	303.5	238.3	-68.5

¹Values expressed as $\mu\text{g./mg. creatinine}$

DISCUSSION

In migrainous subjects with reserpine-induced headaches, there was a consistent rise in urinary histidine excretion comparable to that associated with spontaneous migraine headaches. In normal subjects, reserpine failed to induce headaches and the effect on histidine excretion was variable and inconsistent. A spontaneous or reserpine-induced headache is consistently associated with elevated histidine excretion, but the converse is not necessarily true. It is thus apparent at once that histidine *qua* histidine is not involved in producing the migraine attack. There is no suggestion of alteration in histidine metabolism in migrainous patients, but rather the observed histidinuria is interpreted as a signpost of some unexplained derangement. Separation of unidentified substances from urinary lysine may prove to be of more interest than the increase in urinary histidine and may have a more direct bearing on the mechanism of migraine.

It is interesting to note that one subject (P.L.) was considered to have migraine and showed a two-fold rise in histidine excretion during spontaneous headache. Administration of 2.5 mg. reserpine failed to induce headache. The urinary histidine level

was unchanged after the injection of reserpine. This observation lends support to the finding that only when the patient experiences a headache does the level of the urinary histidine rise. The failure of this patient to develop headache after reserpine is probably related to the dose. A higher dose may be necessary to induce headache in some individuals. This patient was the only migrainous individual who failed to develop headache after 2.5 mg. reserpine intramuscularly.

The increased excretion of histidine and possibly other basic substances during headache may reflect either a pre-renal or renal phenomenon. Possibly the aminoaciduria is related to the breakdown of a polypeptide, which may participate in producing attacks of migraine. Perhaps the aminoaciduria reflects saturation by an unidentified substance of enzyme sites in the renal tubules responsible for the active transport of amino acids. Both of these suggestions are of course purely speculative at the present time. Measurement of plasma levels of basic amino acids may shed some light on the problem.

Many factors operating during migraine attacks, *e.g.*, emotional response and the influence of adrenal stimulation, have for the purposes of the study been neglected. Whatever the mechanism, it appears reasonable to conclude that the effect of reserpine on histidine excretion in migrainous patients is a real one, and that the data permit, at least for the purpose of further systematic study, a biochemical distinction between migrainous and non-migrainous individuals.

SUMMARY

Twenty patients were studied: seven normals, five with spontaneous migraine, and eight with reserpine-induced headaches. Increases in histidine excretion were found to accompany both spontaneous and reserpine-induced headache. The effect of reserpine on migraine appears to be a useful instrument for biochemical and clinical study.

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REFERENCES

- Kimball, R. W., and Bauer, S. (1966). A comparison of effects of ethyl alcohol and reserpine on migraine. To be published.
- Kimball, R. W., and Friedman, A. P. (1961). Studies on the pathogenesis of migraine. In *Recent Advances in Biological Psychiatry*, vol. 3, edited by J. Wortis, pp. 200-207. Grune and Stratton, New York.
- Menkes, J. H. (1964). Personal communication.
- Moore, S., and Stein, W. H. (1954). A modified ninhydrin reagent for the photometric determination of amino acids and related compounds. *J. biol. Chem.*, **211**, 907-913.
- Snedecor, G. W. (1956). *Statistical Methods*, 5th ed., pp. 46-47. Iowa State College Press, Ames, Iowa.
- Wolff, H. G. (1963). *Headache and Other Head Pain*, 2nd ed., pp. 318-326. Oxford University Press, New York.